

We claim:

1. A device for monitoring the migration or invasion of a biological particle such as a cell, which device comprises:
 - a) an upper chamber adapted to receive and retain a cell sample;
 - b) a lower chamber comprising at least two electrodes; and,
 - c) a biocompatible porous membrane having a porosity sufficient to allow cells to migrate therethrough, wherein said membrane is disposed in the device so as to separate the upper and lower chambers from one another;

wherein migration of cells through the porous membrane permits contact between the migrating cells and one or more electrodes of said lower chamber, and wherein further said contact provides a detectable change in impedance between or among the electrodes.
2. The device according to Claim 1, wherein the electrodes are disposed on the bottom surface of the lower chamber.
3. The device according to Claim 2, wherein the lower chamber has a bottom surface area sufficient for attachment of a grouping of cells selected from the groupings consisting of 1-10, 10-100, 100-300, 300-700, 100-1000, 700-1,000, 1,000-3,000, 3,000-6,000, 6,000-10,000 and 1000-10000 cells.
4. The device according to Claim 2, wherein the electrodes cover at least 5% of the bottom surface area of the lower chamber.
5. The device according to Claim 2, wherein the bottom surface area of the lower chamber is less than 1 mm².
6. The device according to Claim 1, further comprising an impedance analyzer in electrical communication with the at least two electrodes.

7. The device according to Claim 1, wherein said biocompatible porous membrane comprises glass, sapphire, silicon, silicon dioxide on silicon, or one or more polymers.
8. The device according to Claim 7, wherein the biocompatible porous membrane has a thickness between 2 microns and 500 microns.
9. The device according to Claim 1, wherein the biocompatible porous membrane further comprises a coating for promoting the attachment of one or more cells thereto.
10. The device according to Claim 1, further comprising
 - a) electrically conductive traces extending from, and in electrical communication with, the at least two electrodes; and,
 - b) connection means for establishing electrical communication between the electrically conductive traces and an impedance analyzer.
11. A method for monitoring the migration or invasion of a cell, the method comprising:
 - a) providing a device according to Claim 1;
 - b) introducing the cells into the upper chamber of the device; and,
 - c) determining whether a change in impedance between or among the electrodes occurs, which a change in impedance between or among the electrodes is indicative of the invasion of, or migration of cells into or through, the biocompatible porous membrane.
12. The method according to Claim 11, further comprising the step of introducing a known or suspected modulator of cell migration to the lower chamber of the device.
13. The method according to Claim 11, further comprising the step of introducing a known or suspected modulator of cell migration to the upper chamber of the device.
14. The method according to Claim 11, wherein the cells are mammalian cells.
15. The method according to Claim 14, wherein the mammalian cells are cells known to be or suspected of being malignant.

16. The method according to Claim 14, wherein the mammalian cells are neuronal cells.
17. The method according to Claim 11, wherein the cells include one or more microorganisms.
18. The device according to Claim 7, wherein the polymers comprise polyimide, polystyrene, polycarbonate, polyvinyl chloride, polyester and polyethylene or urea resin.
19. The device according to Claim 8, wherein the biocompatible porous membrane has a thickness between 5 microns and 50 microns.
20. The device according to Claim 1, wherein the biocompatible porous membrane comprises at least one hole having a diameter between about 1 micron and about 25 microns.
21. The device according to Claim 1, wherein the electrodes are disposed on the bottom surface of the membrane.
22. The device according to Claim 21, wherein the biocompatible porous membrane further comprises a layer of epithelial or endothelial cells on the upper side of the membrane.
23. The device according to Claim 1, wherein the electrodes comprise gold, silver, platinum, chromium, aluminum, copper, indium tin oxide, or titanium.
24. A device for measuring electrical impedance, resistance, or capacitance of a cell/substrate interface, comprising two or more electrodes fabricated on one side of a biocompatible membrane that comprises at least one pore, wherein said device has a surface suitable for cell attachment or growth.

25. The device according to Claim 24, wherein said biocompatible membrane comprises glass, sapphire, silicon, silicon dioxide on silicon, one or more plastics, or one or more polymers.

26. The device according to Claim 25, wherein said biocompatible membrane comprises polyimide, polycarbonate, or polyester.

27. The device according to Claim 24, wherein the thickness of said membrane is from about 2 microns to about 500 microns.

28. The device according to Claim 25, wherein said biocompatible membrane comprises a coating that allows the attachment of one or more cells.

29. The device according to Claim 28, wherein said coating comprises an extracellular matrix component.

30. The device according to Claim 24, wherein said at least one pore has a diameter that does not permit the passage of cells used in the measuring electrical impedance, resistance, or capacitance of a cell/substrate interface through the pore.

31. The device according to Claim 24, wherein said at least one pore has a diameter of less than about 1 micron.

32. The device according to Claim 24, wherein said at least one pore has a diameter that permits the passage of a migrating or invasive cell used in the measuring electrical impedance, resistance, or capacitance of a cell/substrate interface through the pore.

33. The device according to Claim 24, wherein said at least one pore has a diameter of between about 1 micron and about 25 microns.

34. The device according to Claim 24, wherein said two or more electrodes comprise gold, silver, platinum, chromium, aluminum, copper, indium tin oxide, steel, or titanium.

35. The device according to Claim 24, wherein said biocompatible membrane has a thickness between 5 microns and 50 microns.

36. The device according to Claim 24, wherein at least two of said two or more electrodes have substantially the same surface area.

37. The device according to Claim 36, wherein the at least two electrodes that have substantially the same surface area are in an interdigitated or concentric configuration.

38. The device according to Claim 36, wherein the at least two electrodes have circle-on-line, diamond-on-line, castellated, or sinusoidal geometries.

39. The device according to Claim 37, wherein the width of the electrodes is from about 20 microns to about 250 microns.

40. The device according to Claim 37, wherein the gap between electrode elements is between about 3 microns and about 80 microns in width.

41. The device according to Claim 37, wherein the gap between electrode elements is between about 0.2 times and about 6 times the width of cells used in the measuring electrical impedance, resistance, or capacitance of a cell/substrate interface.

42. The device according to Claim 37, wherein the ratio of the gap width to the electrode structure width ranges from about 1 : 20 to about 1 : 1.

43. The device according to Claim 36 situated in a fluid container.

44. The device according to Claim 43, further comprising an impedance analyzer connected to the at least two electrodes.

45. The device according to Claim 44, wherein, in the presence of a conducting solution, the attachment or detachment of one or more cells on the side of the membrane on which the at least two electrodes are fabricated can be detected by a change in impedance using the device.

46. The device according to Claim 45, wherein the exposed surface area of the side of the biocompatible membrane on which said electrodes are fabricated comprises an approximately uniform distribution of electrode elements.

47. The devices according to Claim 46, wherein said electrodes are distributed over at least 50% of the exposed surface area of the side of the biocompatible membrane on which two or electrodes are fabricated.

48. The devices according to Claim 47, wherein said electrodes are distributed over at least 90% of the exposed surface area of the side of the biocompatible membrane on which two or more electrodes are fabricated.

49. The device according to Claim 24, wherein said two or more electrodes comprise at least four electrodes.

50. The device according to Claim 49, wherein the at least four electrodes are arranged in an electrode structure array of two or more interdigitated electrode structure units (IDES) or concentric electrode structure units (CCES), each of which comprises at least two electrodes.

51. A device comprising the device of Claim 50, wherein said biocompatible membrane is reversibly or irreversibly attached to a structure that provides a plurality of isolated fluid containers such that at least one of the fluid containers comprises a single IDES or CCES structure unit.

52. The device according to Claim 51, wherein, for each of said plurality of isolated fluid containers that comprises a single IDES or CCES, the exposed surface area of said one side of said biocompatible membrane on which electrodes are fabricated comprises an approximately uniform distribution of electrodes or electrode elements.

53. A system for measuring electrical impedance, resistance, or capacitance of a cell/substrate interface comprising the device of Claim 52, further comprising an impedance analyzer connected to the at least four electrodes.

54. The device according to Claim 43, wherein the device separates an upper chamber from a lower chamber of the fluid container.

55. The device according to Claim 54, wherein the at least two electrodes are fabricated on the upper side of said membrane.

56. The device according to Claim 55, wherein said at least one pore has a diameter of less than about 1 micron.

57. The device according to Claim 55, wherein said membrane comprises a layer of Caco-2 cells on the upper side of said membrane.

58. The device according to Claim 55, wherein said membrane comprises a layer of epithelial or endothelial cells on the upper side of said membrane.

59. The device according to Claim 55, wherein said membrane comprises at least one biomolecular coating or extracellular matrix component on the upper side of said membrane.

60. The device according to Claim 58, wherein the device is used to assay the migration or invasiveness of one or more cells through said layer of epithelial cell or endothelial cells and the lower chamber comprises at least one compound known to modulate the migration or invasiveness of said one or more cells or at least one compound suspected of modulating the migration or invasiveness of said one or more cells.

61. The device according to Claim 58, wherein the device is used to assay the migration or invasiveness of one or more cells through said layer of epithelial cell or endothelial cells and the upper chamber comprises at least one compound known to modulate the migration or invasiveness of said one or more cells or at least one compound suspected of modulating the migration or invasiveness of said one or more cells.

62. The device according to Claim 54, wherein said at least two electrodes are fabricated on the lower side of said membrane.

63. The device according to Claim 62, wherein said at least one pore has a diameter of between about 1 micron and about 25 microns.

64. The device according to Claim 62, wherein said membrane comprises at least one substance that promotes cell adhesion on the lower side of said membrane.

65. The device according to Claim 62, wherein said membrane comprises at least one biomolecular coating or extracellular matrix component on the upper side of said membrane.

66. The device according to Claim 62, wherein said membrane comprises a layer of epithelial or endothelial cells on the upper side of said membrane.

67. The device according to Claim 62, wherein said device is used to assay the migration or invasiveness of one or more cells.

68. The device according to Claim 67, wherein said lower chamber comprises at least one compound known to modulate the migration or invasiveness of cells, or at least one compound suspected of modulating the migration or invasiveness of cells.

69. The device according to Claim 67, wherein said upper chamber comprises at least one compound known to modulate the migration or invasiveness of cells, or at least one compound suspected of modulating the migration or invasiveness of cells.

70. An apparatus for measuring electrical impedance, resistance, or capacitance of a cell/substrate interface, comprising a plate that comprises two or more wells, at least two of which comprises the device of Claim 24, wherein each device separates each well into upper and lower chambers.

71. The apparatus according to Claim 70, wherein the two or more electrodes are on the lower side of the membrane.

72. The apparatus according to Claim 70, wherein the two or more electrodes are on the upper side of the membrane.

73. An apparatus for measuring electrical impedance, resistance, or capacitance of cell/substrate interface comprising the device of Claim 52, wherein the biocompatible membrane is reversibly or irreversibly attached to a first plate that comprises two or more wells that provide lower chambers of cell migration units and is reversibly or irreversibly attached to a second plate that provides tube structures that provide upper chambers of cell migration units, such that each cell migration unit comprises a single IDES or CCES.

74. The apparatus according to Claim 73, wherein said electrode structure array is on the lower side of said biocompatible membrane.

75. The apparatus according to Claim 73, wherein said electrode structure array is on the upper side of said biocompatible membrane.

76. The apparatus according to Claim 75, wherein said biocompatible membrane comprises a layer of Caco-2 cells on the upper side of said biocompatible membrane.

77. The apparatus according to Claim 75, wherein said biocompatible membrane comprises a layer of epithelial or endothelial cells on the upper side of said biocompatible membrane.

78. An apparatus for measuring electrical impedance, resistance, or capacitance of a cell/substrate interface, comprising: .

a) a plate that comprises two or more wells; and

b) an insert tray that fits said plate,

wherein said insert tray comprises one or more insert chambers, each of which comprises:

i) fluid impermeable walls; and

ii) the device of Claim 24 forming the bottom of each of said one or more insert chambers;

further wherein each insert chamber fits into a well of said plate such that the wells of the plate form a lower chamber and the insert forms an upper chamber of a cell invasion/migration unit.

79. The apparatus according to Claim 78, wherein said at least two electrodes are fabricated on the upper side of said biocompatible membrane.

80. The apparatus according to Claim 79, wherein said at least one pore has a diameter of less than about 1 micron.

81. The apparatus according to Claim 79, wherein said biocompatible membrane comprises a layer of Caco-2 cells on the upper side of said biocompatible membrane.

82. The apparatus according to Claim 79, wherein said membrane comprises a layer of epithelial or endothelial cells on the upper side of said biocompatible membrane.
83. The apparatus according to Claim 79, wherein said membrane comprises at least one biomolecular coating or extracellular matrix component on the upper side of said biocompatible membrane.
84. The apparatus according to Claim 82, wherein said device is used to assay the migration or invasiveness of one or more cells through said layer of epithelial or endothelial cells and said lower chamber comprises at least one compound known to modulate the migration or invasiveness of said one or more cells, or at least one compound suspected of modulating the migration or invasiveness of said one or more cells.
85. The apparatus according to Claim 82, wherein said device is used to assay the migration or invasiveness of one or more cells through said layer of epithelial or endothelial cells and said upper chamber comprises at least one compound known to modulate the migration or invasiveness of said one or more cells, or at least one compound suspected of modulating the migration or invasiveness of one or more cells.
86. The apparatus according to Claim 78, wherein the at least two electrodes are fabricated on the lower side of said biocompatible membrane.
87. The apparatus according to Claim 86, wherein said at least one pore has a diameter of between about 1 micron and about 25 microns.
88. The apparatus according to Claim 86, wherein said membrane comprises at least one substance that promotes cell adhesion on the lower side of said membrane.

89. The apparatus according to Claim 86, wherein said membrane comprises at least one biomolecular coating or extracellular matrix component on the upper side of said membrane.

90. The apparatus according to Claim 86, wherein said membrane comprises a layer of epithelial or endothelial cells on the upper side of said membrane.

91. The apparatus according to Claim 86, wherein said device is used to assay the migration or invasiveness of one or more cells. .

92. The apparatus according to Claim 91, wherein said lower chamber comprises at least one compound known to modulate the migration or invasiveness of cells, or at least one compound suspected of modulating the migration or invasiveness of cells.

93. A method for monitoring cell migration or invasion, comprising:
a) providing an apparatus of claim 53;
b) placing cells in the upper chamber of said apparatus ; and
c) monitoring a change of impedance between or among the electrodes to monitor migration or invasion of said cells.

94. The method according to Claim 93, further comprising adding a known or suspected modulator of cell migration or cell invasion to the lower chamber of said apparatus.

95. The method according to Claim 93, further comprising adding a known or suspected modulator of cell migration or cell invasion to said upper chamber of said apparatus.

96. A method for monitoring cell migration or invasion, comprising:
a) providing an apparatus of claim 73;
b) placing cells in the upper chamber of said apparatus ; and
c) monitoring a change of impedance between or among the electrodes to monitor migration or invasion of said cells.

97. The method according to Claim 96, further comprising adding a known or suspected modulator of cell migration or cell invasion to the lower chamber of said apparatus.

98. The method according to Claim 96, further comprising adding a known or suspected modulator of cell migration or cell invasion to said upper chamber of said apparatus.

99. A method for monitoring cell migration or invasion, comprising:

- a) providing an apparatus of claim 78;
- b) placing cells in the upper chamber of said apparatus ; and
- c) monitoring a change of impedance between or among the electrodes to monitor migration or invasion of said cells.

100. The method according to Claim 99, further comprising adding a known or suspected modulator of cell migration or cell invasion to the lower chamber of said apparatus.

101. The method according to Claim 99, further comprising adding a known or suspected modulator of cell migration or cell invasion to said upper chamber of said apparatus.

102. An apparatus for monitoring cell migration or invasion, which apparatus comprises:

- a) an upper chamber for placing migrating or invasive cells or cells suspected of being migrating or invasive, said upper chamber comprising an electrode;
- b) a lower chamber comprising an electrode;
- c) a polymer membrane comprising multiple holes of a suitable size allowing said migrating or invasive cells to go through, said membrane connected to said upper and lower chambers and separating said upper chamber and lower chamber from each other,

wherein said migrating or invasive cells move through said holes of said membrane which results in a change of impedance between said electrodes in said upper and lower chamber that can be used to monitor migration or invasion of said cells.

103. The apparatus according to Claim 102, wherein the lower chamber has a bottom surface area sufficient for attachment of about 1-10, 10 –100, 100-300, 300-700, 100 – 1000, 700-1,000, 1,000-3,000, 3,000-6,000, 6,000-10,000 or 1000-10000 cells.

104. The apparatus according to Claim 102, wherein the electrode(s) in the lower chamber is or are on the bottom surface of the lower chamber.

105. The apparatus according to Claim 102, wherein the electrode(s) in the lower chamber is or are on the side of the lower chamber.

106. The apparatus according to Claim 102, wherein the electrode(s) comprises an electrode array having at least two electrode elements.

107. The apparatus according to Claim 106, wherein the electrode(s) has a shape selected from the group consisting of a rectangle, a circle, a circle on a rectangular line and a sinusoidal line.

108. The apparatus according to Claim 102, wherein the polymer membrane comprises multiple holes of a same size.

109. The apparatus according to Claim 102, wherein the polymer membrane comprises multiple holes of different sizes.

110. The apparatus according to Claim 102, wherein the lower chamber comprises a modulator of cell migration or invasion.

111. The apparatus according to Claim 102, wherein the upper chamber comprises a modulator of cell migration or invasion.

112. The apparatus according to Claim 102, which further comprises an impedance analyzer.

113. A method for monitoring cell migration or invasion, which method comprises:

- a) providing an apparatus of claim 102;
- b) placing migrating or invasive cells or cells suspected of being migrating or invasive on the upper chamber for said apparatus and allowing said cells to move from said upper chamber into said lower chamber via said holes of said polymer membrane; and
- c) monitoring a change of impedance between or among the electrodes to monitor migration or invasion of said cells.

114. The method according to Claim 113, wherein the amount or number of cells that migrate or invade into the lower chamber is monitored based on the monitored impedance.

115. The method according to Claim 113, wherein the cell migration or invasion is monitored in the presence and absence of a test compound and the method is used to determine whether said test compound modulates migration or invasion of the cells.

116. The method according to Claim 113, wherein the cell migration or invasion is stimulated by a migration or invasion stimulator and the method is used to screen the test compound for an antagonist of said stimulator.
117. The device of Claim 55, wherein the pores of said biocompatible membrane have a diameter of less than about 3 microns.
118. The device of Claim 117, further comprising an impedance analyzer.
119. A method of measuring the integrity of a cell monolayer, comprising:
culturing cells in the upper chamber of the device of Claim 118; and
monitoring the integrity of the cell monolayer in said at least one chamber by monitoring the impedance between said electrodes fabricated on said membrane using said impedance analyzer .
120. The method according to Claim 119, wherein said cells are intestinal epithelial cells.
121. The method according to Claim 120, wherein said cells are Caco-2 cells.
122. A system for measuring electrical impedance, resistance, or capacitance of cell/substrate interface, comprising:
a) the apparatus of Claim 73;
b) an impedance analyzer;
c) interface electronics comprising electronic switches to control and switch said at impedance analyzer to different electrode structure units of said apparatus.
123. The system according to Claim 122, further comprising software that can enable real time measurement or monitoring of impedance between the electrodes or electrode structures of said apparatus.

124. The system of claim 123, wherein said software has at least one of the following functions:

- (a) controlling electronic switching for connecting said impedance analyzer to one of multiple electrode structure units of the present apparatuses;
- (b) controlling impedance analyzer for measurement of impedance between or among electrode structures at one or multiple frequencies;
- (c) processing the acquired impedance data to derive appropriate biologically relevant parameters (e.g., cell number index);
- (d) displaying the results on a monitor or storing results; and
- (e) automatically performing above functions 1 through 4 at regular or irregular time intervals.

125. The apparatus according to Claim 78, wherein said one or more insert chambers are two or more insert chambers.

126. A system for measuring electrical impedance, resistance, or capacitance of cell/substrate interface, comprising:

- a) the apparatus of Claim 125;
- b) an impedance analyzer;
- c) interface electronics comprising electronic switches to control and switch said at impedance analyzer to different electrode structure units of said apparatus.

127. The system of Claim 126, further comprising software that can enable real time measurement or monitoring of impedance between the electrodes of said apparatus.

128. The system of Claim 127, wherein said software has at least one of the following functions:

(a) controlling electronic switching for connecting said impedance analyzer to one of multiple electrode structure units of the present apparatuses;

(b) controlling impedance measurement circuit (or analyzer) for measurement of impedance between or among electrodes at one or multiple frequencies;

(c) processing the acquired impedance data to derive appropriate biologically relevant parameters (e.g., molecular reaction index, or cell number index);

(d) displaying the results on a monitor or storing results; and

(e) automatically performing above functions 1 through 4 at regular or irregular time intervals.

129. The device of Claim 2, wherein said porous membrane has pores of a diameter of less than about 3 micron.

130. The device of Claim 129, further comprising an impedance analyzer.

131. A method for performing a cytotoxicity assay, comprising:

a) culturing cells in the upper chamber of the device of Claim 130;

b) culturing cells in the lower chamber of said device;

c) adding one or more compounds to be tested for toxicity to said upper chamber;

d) monitoring the impedance between the electrodes on the bottom surface of the lower chamber to measure the physiological status of the cells cultured in the lower chamber using said impedance analyzer to assess the cytotoxicity of said one or more compounds.

132. The method of Claim 131, wherein the cells cultured in said upper chamber are cells that can metabolize or derivatize a compound.

133. The method of Claim 132, wherein the cells cultured in said upper chamber are liver cells or intestinal cells.

134. The method of Claim 133, wherein said cells cultured in said lower chamber are cells whose growth, attachment, secretory, or electrophysiological function can be affected by a toxic compound.
135. The method of Claim 134, wherein said cells cultured in the lower chamber are liver cells, heart cells, or neural cells.
136. The device of Claim 130, further comprising electrodes fabricated on the upper surfaces of said biocompatible porous membrane.
137. A method for performing a cytotoxicity assay, comprising:
- a) culturing cells in the upper chamber of the device of Claim 136;
 - b) culturing cells in the lower chamber of the device;
 - c) monitoring the integrity of the cell monolayer in the upper chamber by monitoring the impedance between said electrodes fabricated on said membrane using said impedance analyzer;
 - d) adding one or more compounds to be tested for toxicity to the upper chamber; and
 - e) monitoring the impedance or resistance between the electrodes on the bottom surface of the lower chamber to measure the physiological status of the cells cultured in the lower chamber using said impedance analyzer to assess the cytotoxicity of said one or more compounds.